Hepatitis in Tropical Settings

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Inflammatory Liver Disease in the Tropics

- Viral Hepatitis—Hepatitis A and Hepatitis E
- Liver Abscess—amebic, pyogenic
- Bacterial—brucellosis
- Spirochetal—leptospirosis, secondary syphilis
- Parasites—schistosomiasis, liver flukes (*Fasciola hepatica, Clonorchis sinensis*)
- Other viruses—Dengue , Yellow fever, CMV, EBV
- Echinococcal liver disease
- Less tropical causes—Hepatitis B and C, alcohol ingestion, acetaminophen intoxication, autoimmune
  - Medications—isoniazid, methotrexate, statins
  - Non-Infectious—hemachromatosis, malignancy

Questions to Answer

- What is endemic to the local area, or area of travel?
- Incubation period?
- Pre-deployment / pre-travel vaccinations or prophylaxis?
- Food and water sources?
- Arthropod exposure/protection?

Case 1

- You are a part of a humanitarian relief mission to Sri Lanka with a deployable medical unit.
- 35 y/o tsunami relief worker from France presents with one week of headache, nausea, and fatigue. Initially she thought it was due to being overworked but for the last day she has had jaundice, dark urine, and vomiting. No hematemasis.
- She is otherwise healthy except for a past hx of infertility, currently not pregnant. Not on any meds. Only surgery was a hysteroscopy.

Case 1-Exam

- Jaundiced female, in mild distress. No rash, scleral icterus, lungs CTA, CV normal, diffuse abdominal tenderness, no distension, liver edge palpable 3 cm below right costal margin.
- ALT-2250 IU/L, AST-2100 IU/L
- T bili-4.2 mg/dL (conj 3.9 mg/dL)
- WBC-12,900 ml^3, Hg/Hct-15 g/dL / 46%,
  Plt-295,000 mm^3
- Electrolytes normal, BUN-31 mg/dL, Cr 1.3 mg/dL

Questions for the patient?

- Incubation period?
  - arrived 5 weeks ago, symptoms for the last week
- Predeployment vaccinations, prophylaxis?
  - HepA, HepB, typhoid, Td, JE, rabies, on mefloquine
- Food and water sources?
  - bottled water (except for first week, 4 weeks ago, had some from local water supply)
  - MREs only
- Arthropod exposure/protection?
  - denies any mosquito bites
  - using DEET, bed netting

Differential Diagnosis

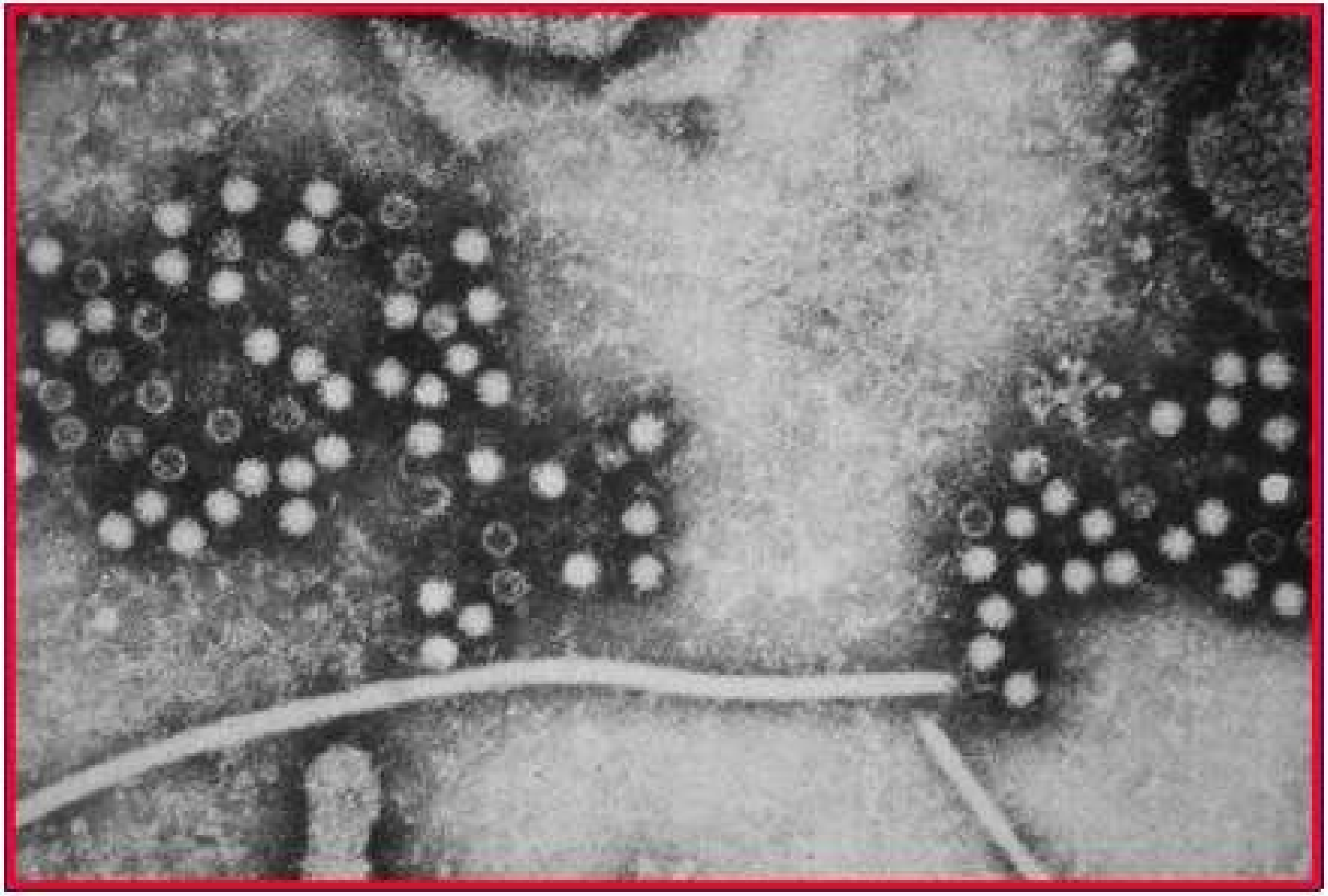
- Hepatitis E
- Hepatitis A

- Typhoid fever, Leptosporosis
- Liver fluke infection
  - *Fasciola hepatica*, *Clonorchis senensis*
- Schistosomiasis
- Hep B
- Hep C
- Toxic ingestion (acetaminophen)

Viral Hepatitides

- Hepatitis A and E
  - transmitted fecal oral
  - typically no chronic disease issues
- Hepatitis B, C, and D
  - transmitted via blood and blood-derived body fluid exposure
  - chronic disease may develop

Hepatitis E Virus

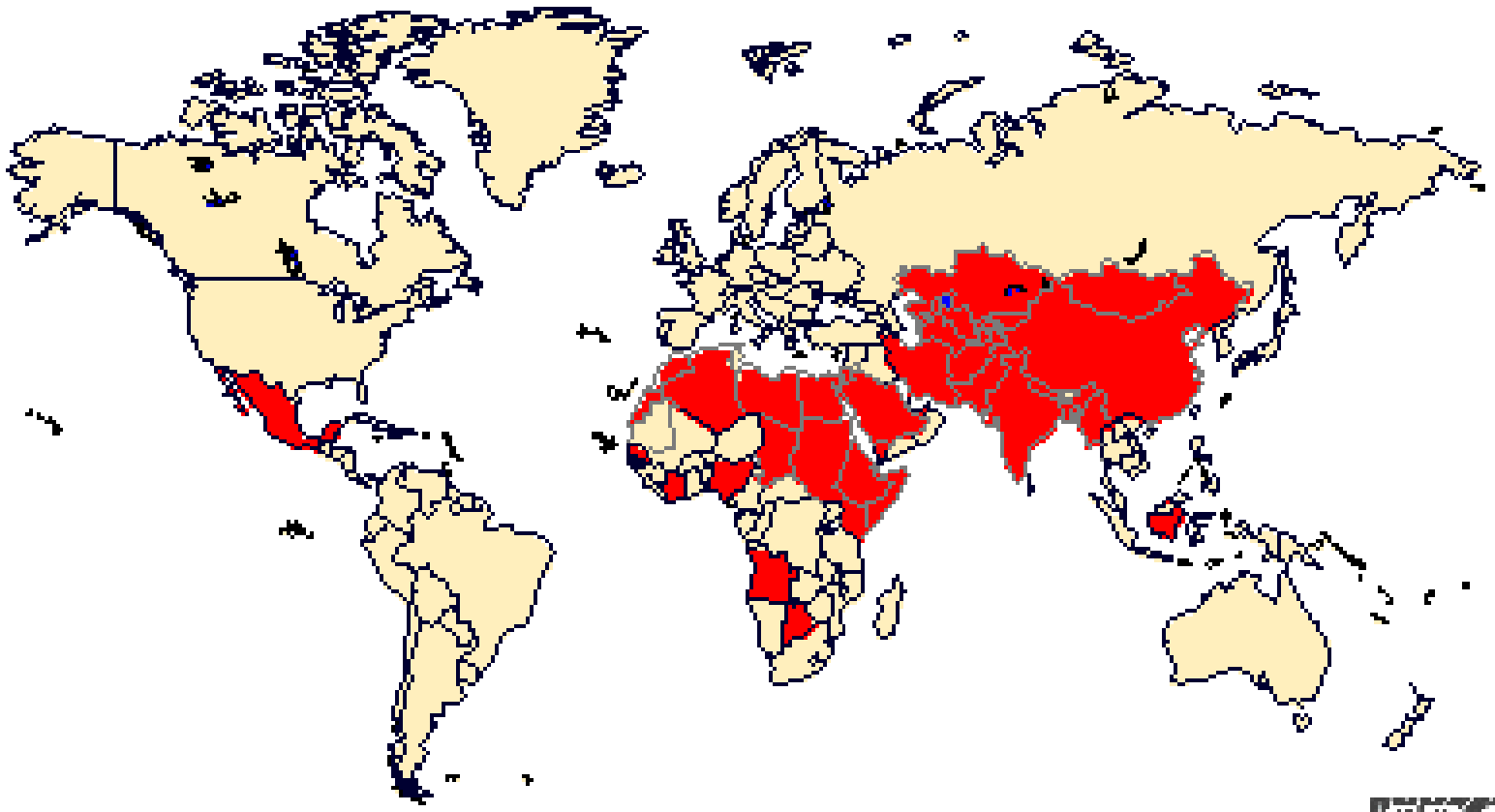


Hepatitis E Virus

- Enterically transmitted non-A, non-B hepatitis
- First identified in 1983
- Similar to HAV, but a different geographic distribution
  - HEV is restricted to tropical/sub-tropical developing countries
- RNA virus
- Transmitted fecal-oral
  - areas of poor sanitation, poor hygiene, and contaminated water supply
  - usually after heavy rains/flooding when water sources become contaminated

Geographic Distribution of Hepatitis E

Outbreaks or Confirmed Infection in > 25% of Sporadic Non-ABC Hepatitis



Hepatitis E-Pathogenesis/Epidemiology

- Most significant impact is on pregnant women
  - mortality rate of 25%, especially in the 2nd and 3rd trimester

Hepatitis E-Clinical Presentation

- Self limited disease
- Similar to HAV infection
- No chronic sequelae of infection
- Incubation of 15-60 days, average 40 days

Hepatitis E-Clinical Presentation

- Acute Icteric Hepatitis most common
  - symptoms insidious in onset
  - flu-like sx, fever, malaise, abdominal pain, anorexia, nausea, aversion to tobacco, diarrhea
  - will develop dark urine, jaundice, and tender hepatosplenomegaly
  - symptoms last 1-4 weeks

Hepatitis E-Clinical Presentation

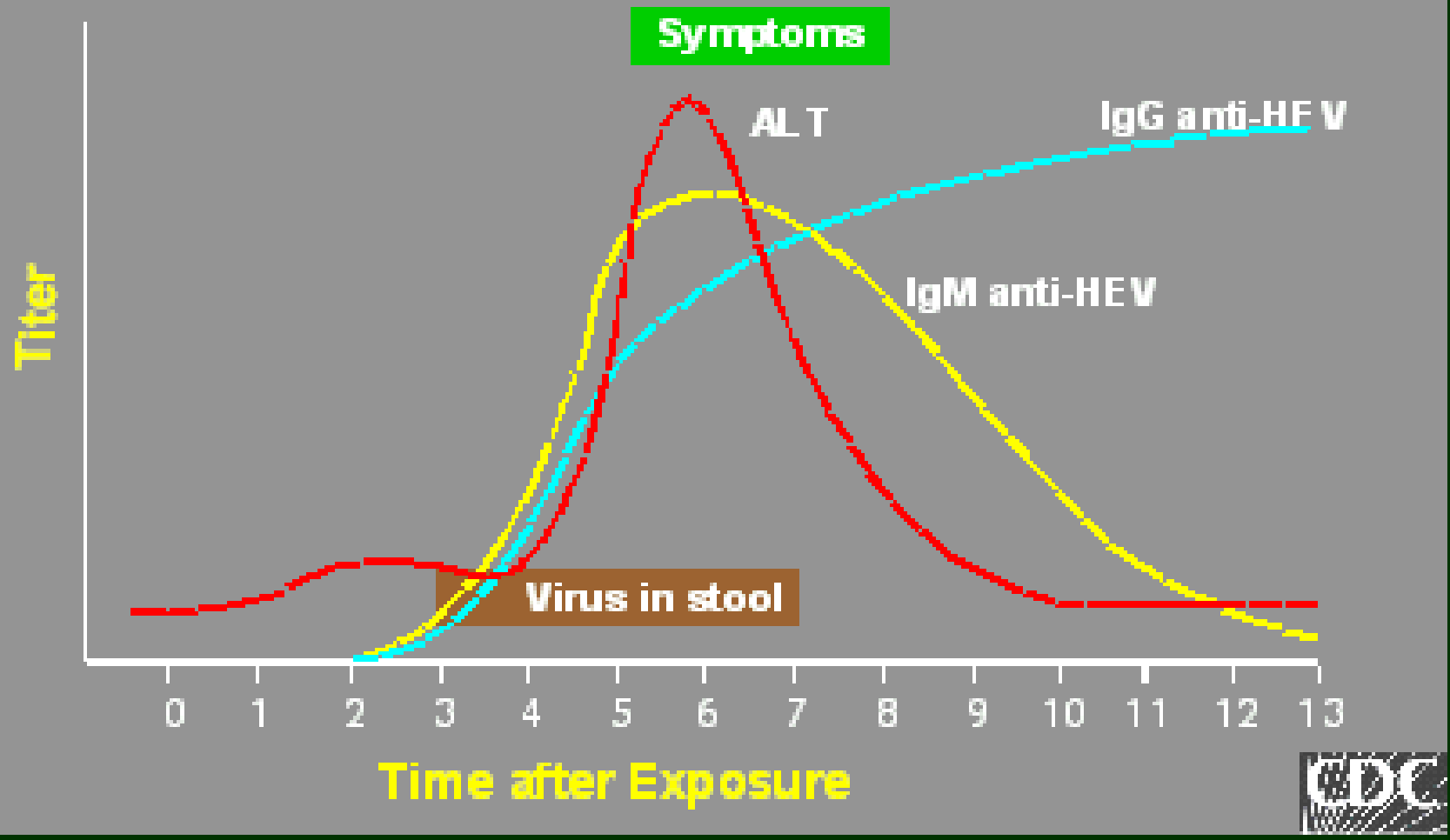
- Cholestatic hepatitis
  - presents with jaundice and itching
  - can last for 2-6 months, and will resolve spontaneously
- Anicteric hepatitis
  - very mild course
  - non-specific flu-like symptoms, no jaundice
- Fulminant, subacute, or late-onset hepatic failure
  - small proportion of infected individuals will have this
  - highest risk in pregnant females (25% mortality rate)
- Overall case-fatality rate of 0.5 to 4%

Hepatitis E-Diagnosis

- anti-HEV IgM present for 3-4 months, and gone by 4-5 months after exposure
- anti-HEV IgG presents within a week after IgM, and remains high for 4-5 years, but eventually diminishes over time
- HEV shed in stools one week prior to onset of symptoms, and persists as long as 2 weeks
- Liver associated enzymes can be elevated 10 days prior to onset of symptoms, and normal by 6 weeks

Hepatitis E Virus Infection

Typical Serological Course



Hepatitis E-Treatment/Prevention

- Treatment
  - Supportive therapy only
  - Similar to HAV infection
- Key to prevention is avoidance of contaminated water
  - drink from water of known purity, boiling water can help

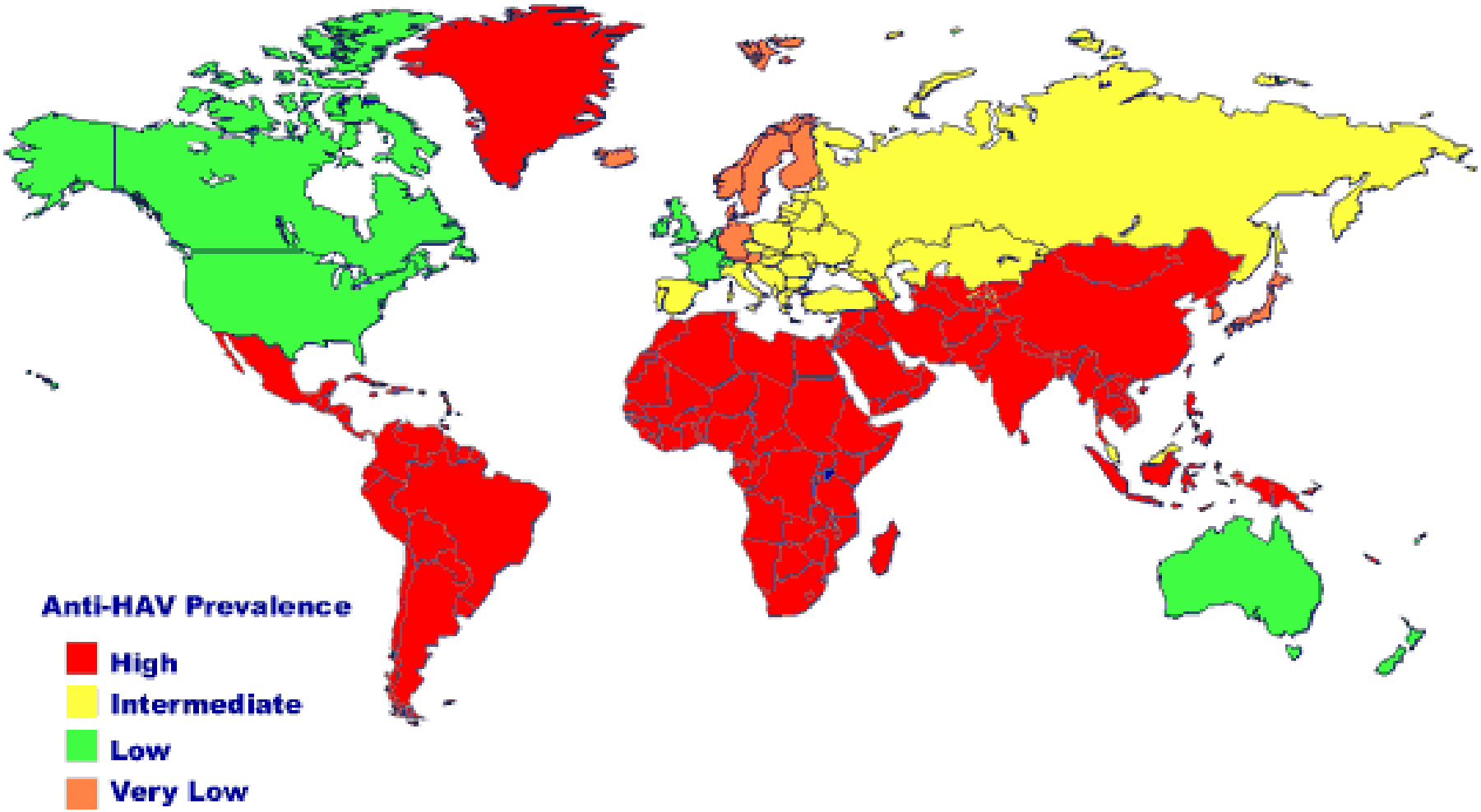
Hepatitis E-Treatment/Prevention

- Passive immunization may be effective
  - commercially available ISG from endemic areas of unknown efficacy
  - because of large outbreaks seen in endemic areas, HEV IgG may not be fully protective or AB level may fall with time to decrease immunity
- Active immunization
  - no current vaccine
  - WRAIR has phase II and phase III trials in Nepal

Hepatitis A

- Most common viral hepatitis in 2001 in U.S.
- Most prevalent in areas of low socioeconomic status and poor sanitation

Geographic Distribution of HAV Infection



Recent Outbreak

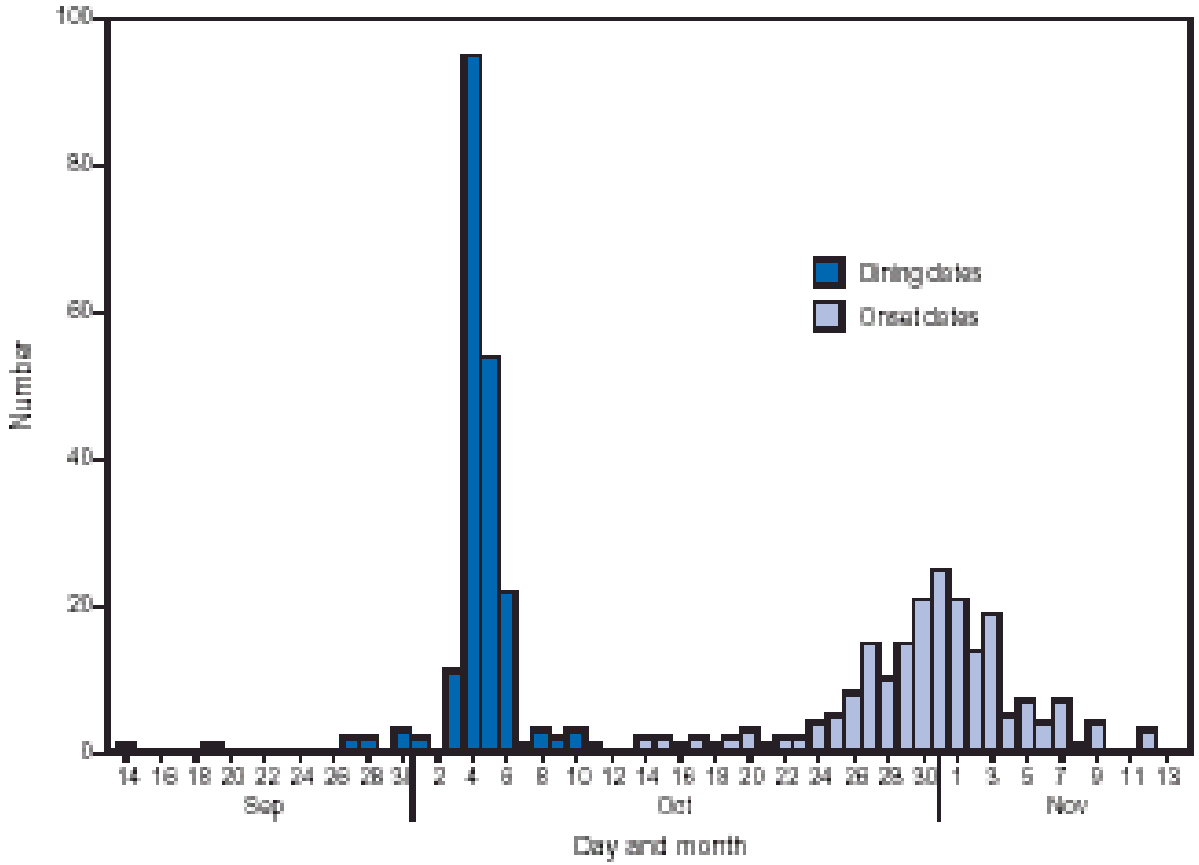
- Pennsylvania restaurant
- 640 people diagnosed with Hep A, Oct/Nov ‘03
  - 13 restaurant food service employees
  - 75 from six other states who dined at this restaurant
  - 3 died
- Outbreak associated with contaminated green onions from Mexico
- Lawsuits

Hepatitis A-Symptoms

- Usually a self-limited, ACUTE, illness
- Rarely fulminant hepatic failure
- Sx will vary with age
- Incubation is 15-50 days (average of 30 days)

- PA outbreak
  - date of onset 14 Oct - 12 Nov
  - date of exposure 14 Sept - 17 Oct (3-6 Oct)

FIGURE. Number of hepatitis A cases*, by date of eating at Restaurant A and illness onset — Monaca, Pennsylvania, 2003



* N = 206. Excludes one case-patient whose illness onset date was not available. Dining dates for three persons who ate at Restaurant A on October 15 (n = one) and October 17 (n = two) are not shown.

MMWR 52:1155-1157. 28 Nov 2003

Hepatitis A-Clinical Presentation

- Classic HAV infection (80% of symptomatic patients)
  - usually asymptomatic in children
  - adults can have a flu-like illness to hepatic failure
  - fatigue, malaise, nausea/vomiting, anorexia, fever, RUQ pain
  - loose taste for tobacco
  - develop dark urine, gray stools, jaundice, pruritus
- Signs
  - hepatosplenomegaly, tender liver, jaundice

Hepatitis A-Clinical Presentation

- Relapsing Hep A infection (4-20%)
  - 2 or more bouts of acute HAV infection over 6-10 weeks
  - sx-free intervals, progressive bouts are milder
- Cholestatic Hep A infection (10%)
  - prolonged course over months
  - fever with marked pruritus and jaundice
  - bilirubin remains elevated with other liver associate enzymes normal

Hepatitis A-Diagnosis

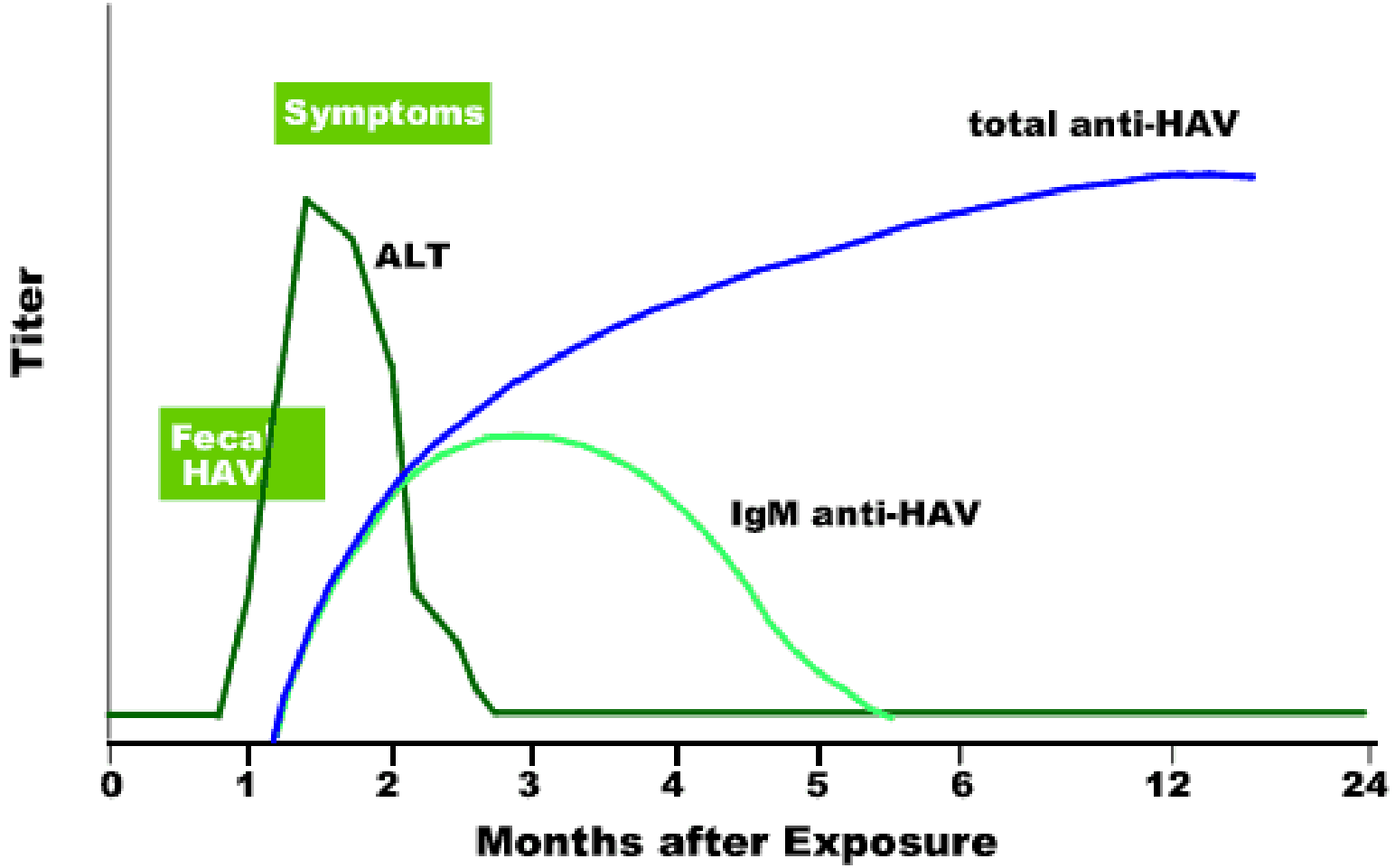
- Clinical syndrome consistent with HAV infection
- Elevated Liver associated enzymes
  - Average ALT=2000, Average AST=1500
  - LAE elevation does not correlate with severity of disease or prognosis

Hepatitis A-Diagnosis

- Detect Anti-HAV AB in serum
  - serum anti-HAV IgM is the gold standard
    - IgM is elevated at 1-2 weeks after exposure, and persists for 3-6 months
  - serum anti-HAV IgG infers prior infection or vaccination
    - IgG is protective (lifelong?)
    - detectable at 5-6 weeks after exposure, persists for decades
- Prolonged PT can be a sign of impending liver failure

Hepatitis A Virus Infection

Typical Serologic Course



Hepatitis A-Treatment

- Acute HAV infection is self-limited
- Treatment is supportive
  - treat dehydration, coagulopathy, encephalopathy, if elderly, or have some other chronic liver disease
  - avoid alcohol and other hepatotoxins (acetaminophen <2gm/day)
- Steroids considered for prolonged cholestatic form of HAV
  - no evidence that this improves outcome
  - may shorten duration of illness

Fulminant Hepatitis A

- 0.35% of adult cases
- Danger signs include excitability, irritability, insomnia, confusion, severe vomiting
- Heralded by worsening jaundice, encephalopathy, and prolonged PT (one week 55%, one month 90%)
- Patients at risk are elderly or have chronic liver disease
- Fatality rate of 2% (others 0.3%, 1.8% if age>50)
- Early referral for liver transplant is required

Hepatitis A-Prevention

- Improve sanitary conditions, hand washing, avoidance of contaminated food/water sources.
- Passive immunization
- Active immunization

Hepatitis A-Prevention

- Passive immunization
  - Immune serum globulin (sterile preparation of concentrated AB made from pooled human plasma)
  - IGIM used for hep A prevention
  - not to be given with live attenuated virus vaccines (MMR, VZV, yellow fever)

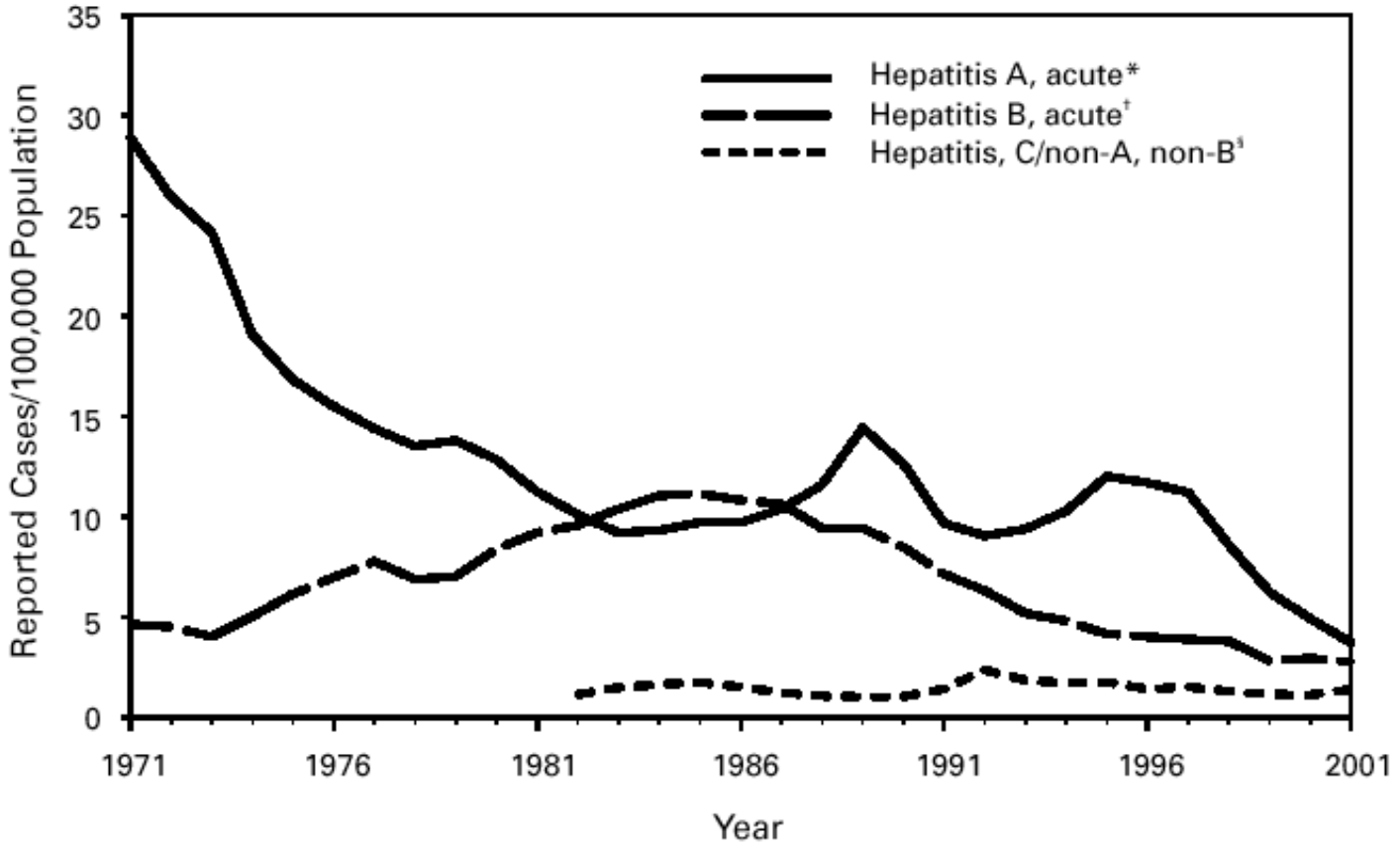
Active immunization

- Two HAV vaccines approved for use
  - HAVRIX and VAQTA, both formalin inactivated
  - both are safe and efficacious
  - protective AB after one month (~90%) and 7 months (~100%)
  - two doses; zero and six months
  - protects 5-10 years (longer?)
  - can give with ISG as HAV vaccine is an inactivated virus

Hepatitis A-Prevention

- HAV vaccine--give to the following
  - kids in areas of the U.S. with rates of infection 2X national average (Native Americans, Native Alaskans)
  - travelers to areas endemic for HAV
    - your military population
  - homosexual males
  - patients with clotting disorders
  - illicit drug users
  - lab techs in HAV research labs
  - patients with chronic liver disease due to HBV, HCV, or before liver transplant

HEPATITIS. Reported cases per 100,000 population, by year — United States, 1971–2001

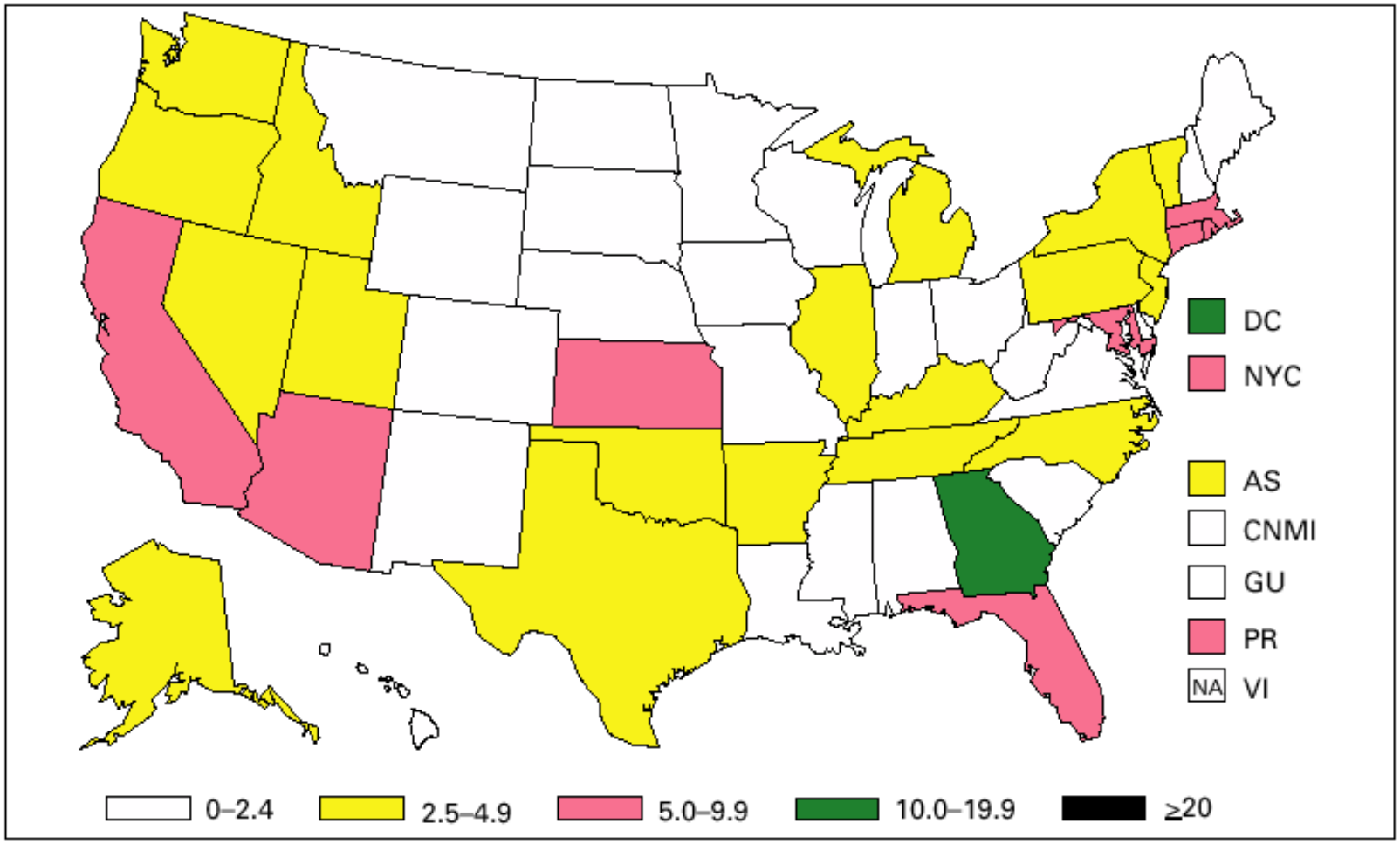


*Hepatitis A vaccine was first licensed in 1995.
† Hepatitis B vaccine was first licensed in June 1982.
§ An anti-HCV (hepatitis C virus) antibody test first became available in May 1990.

In 2001, the hepatitis A rate was the lowest ever recorded. However, cyclic increases in hepatitis A have been observed approximately every 10 years, and thus rates could increase again. The incidence of hepatitis B continues to decline, but because of asymptomatic infections and underreporting, reported cases represent only a fraction of actual infections occurring (approximately 78,000 new infections in 2001). The trend in reported hepatitis C; non-A, non-B after 1990 is misleading because reported cases have included those based only on a positive laboratory test for anti-HCV, and most of these cases represent chronic HCV infection.

MMWR 50:1-108, 2 May 2003

HEPATITIS A. Reported cases per 100,000 population — United States and U.S. territories, 2001



Hepatitis A rates have declined in all regions of the United States, including the western states where rates have historically been higher than elsewhere in the country. Because hepatitis A rates vary from year to year with nationwide increases approximately every 10 years, further monitoring is needed to determine whether these rates will remain low.

MMWR 50:1-108, 2 May 2003

Hepatitis A

- Texas immunization requirements

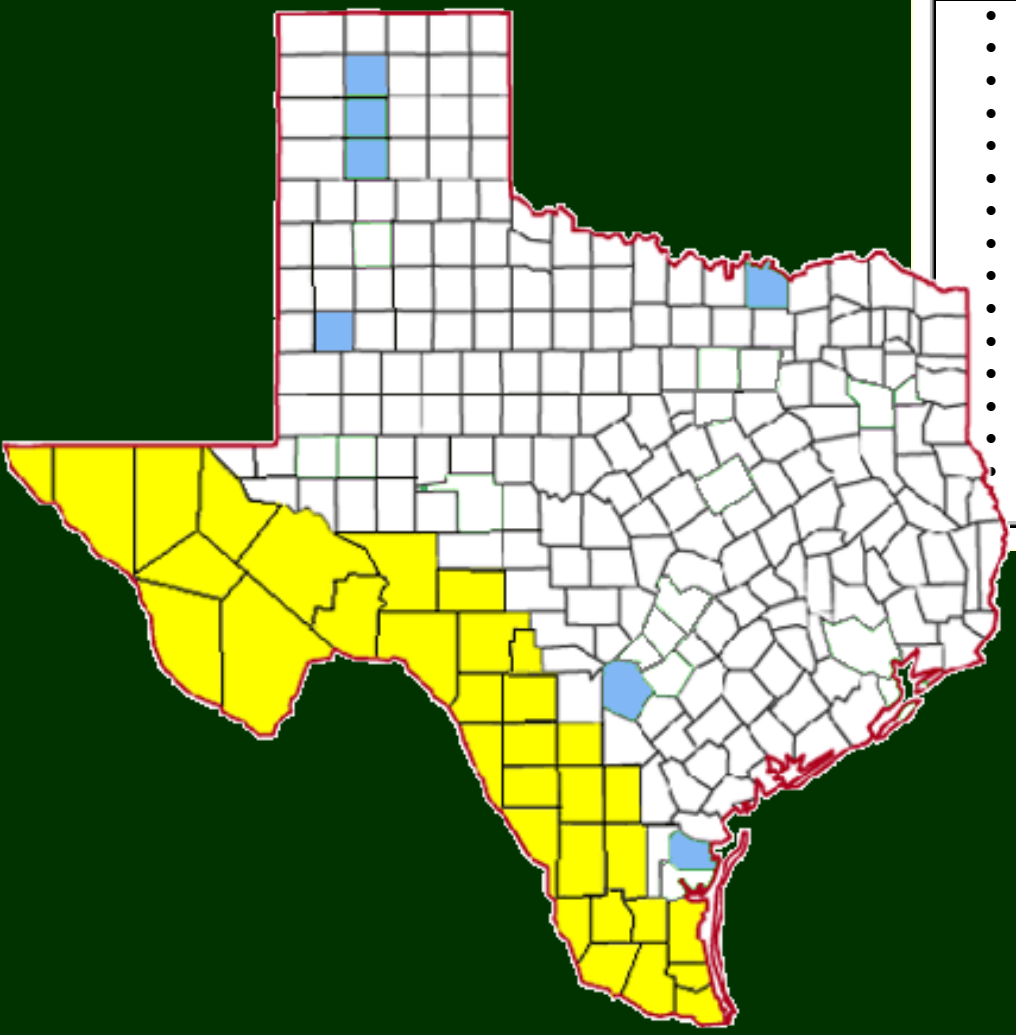
15 mos. through 4 years

Effective 8/1/03-7 counties in addition to 32 border counties, require hepatitis A vaccine.

2 years - One dose hepatitis A vaccine;
3 through 4 years - 2 doses of hepatitis A vaccine (1st dose on or after 2nd birthday)
Three doses polio vaccine
Four doses DTP/DTaP (Fourth dose not required until 18 months.)
One dose Hib vaccine on or after 15 months of age, unless a primary series and booster[g] have been completed
One dose MMR vaccine received on or after 1st birthday[b]
One dose of varicella vaccine received on or after 1st birthday[c]

Hepatitis A vaccine (selected counties)[d]:
2 years-One dose of hepatitis A vaccine;
3 through 4 years-Two doses of hepatitis A vaccine (1st dose on or after 2nd birthday

Hepatitis A
Texas immunization requirements



Original 32 Border Counties		As of August 1, 2003
• Brewster • Brooks • Cameron • Crockett • Culberson • Dimmitt • Duval • Edwards • El Paso • Frio • Hidalgo • Hudspeth • Jeff Davis • Jim Hogg • Kenedy • Kinney	• La Salle • Maverick • McMullen • Pecos • Presidio • Real • Reeves • Starr • Sutton • Terrell • Uvalde • Val Verde • Webb • Willacy • Zapata • Zavala	• Bexar • Grayson • Moore • Nueces • Potter • Randall • Terry

Hepatitis A Virus is the most common vaccine-preventable illness among

References

Viral Hepatitis A, in Control of Communicabel Diseases Manual, James Chin Editor, 17th ed, 2000.

Stapleton JT. Host immune response to Hepatitis A virus. J Infect Dis. 1995;171(Sup1):S9-14.

Tong MJ, El-Farra NS, Grew MI. Clinical manifestations of Hepatitis A: Recent experience in a community teaching hospital. J Infect Dis. 1995:171(Sup1):S15-8.

Prevention of Hepatitis A Through Active or Passive Immunization: Recommendations of the Advisory Committee on Immunization Practices (ACIP), MMWR 48:1-37. 1 October 1999.

Hepatitis A Outbreak Associated with Green Onions at a Restaurant --- Monaca, Pennsylvania, 2003, MMWR 52:1155-1157, 28 Nov 2003.

Case 2

- 47 y/o WM with a 4 day hx of crampy abdominal pain and one day of fever to 102.8 F
  - diarrhea, no hematochezia
  - no vomiting
  - Treated in the ER symptomatically with doxycycline for possible rickettsial disease and sent home
  - improved for one day
- Presents 2 days later with new headache, continuing fever, and worsening nausea and intractable vomiting

Case 2 (continued)

- Recent travel to Brazil, for a fishing expedition on the Amazon River
  - slept in an air conditioned boat
  - wore DEET impregnated clothes while fishing
  - no medical consultation prior to travel
  - no vaccinations, no prophylactic medications
- Other people who traveled with him are not ill

Questions for the patient?

- Incubation period?
  - returned 2 weeks ago from the Amazon
- Predeployment vaccinations, prophylaxis?
  - no vaccinations, minimal PPM
- Food and water sources?
  - bottled water and food supplied by the outrigger
  - “anything I could find in the city”
- Arthropod exposure/protection?
  - multiple mosquito bites despite PPM

Case 2 (continued)

- Information on the outfitter's website stated, "The International medical community suggests yellow fever and malaria prophylaxis for the Amazon region. This is not a requirement to enter Brazil, but merely a suggestion."
- A brochure from the group's travel agent stated, "We do not suggest any inoculations of any kind for this trip....But to make sure you are worry free, consult with your p
physician."

Case 2 (continued)

- Admitted and ill-appearing on exam, with jaundice, and tender hepatomegally.
  - Labs WBC-2300 mm^3, Hg/Hct- 10.5 mg/dL / 31%, Plt-36K
  - PT- 29, INR- 6.3, BUN-65 mg/dL, Cr-5.5 mg/dL
  - ALT-7,600 IU/L, AST-13,700 IU/L, T Bili- 3.3 mg/dL
- Treated presumptively for malaria, no improvement
  - smears negative
  - PCR for malaria also negative
- Broad spectrum antimicrobials, no improvement

Differential Diagnosis

- Arbovirus
  - yellow fever, dengue fever, venezuelan equine encephalitis
- Rickettsial spotted fever
- Leptospirosis
- Hepatitis A or Hepatitis E
  - rare fulminant presentation
- Typhoid fever

Yellow Fever

- Serum from day 2 was negative for YF IgM / IgG
  - also negative on days 3 through 7
- Serum from days 4, 5, 7 and a post-mortem liver tissue sample positive for YF virus RNA by PCR

Yellow Fever

- Arthropod-borne infection
  - *Aedes aegypti*
  - Jungle cycle carried by *Haemagogus* and *Sabethes* mosquitos
- Flavivirus
  - RNA virus
  - originated in Africa, exists in sub-Saharan Africa and S. America. Never documented in Asia
- 50-300 annual cases in S. America
- 4000 annual cases in Africa

Clinical Features of Yellow Fever
Acute Phase

- Incubation 3-6 days
- Broad spectrum of disease—mild to fulminant
  - usually begins with fever, chills, server headache, lumbosacral pain, myalgias, anorexia, nausea and vomitning, minor gingival hemorrhages
  - Faget's sign- bradycardia despite rising fever
  - 3 days of symptoms, followed by brief defervescence
  - return of fever and symptoms with vomiting, epigastric pain, prostration, and jaundice

Clinical Features of Yellow Fever

Hemorrhagic Phase

- coffee ground hematemeis (vomito negro), melana, petechiae, ecchymoses
- volume depletion due to plasma leakage
- renal failure
- liver failure manifested by elevated transaminases and loss of synthetic function
- death (in 20-50% of severe cases) at day 7-10

Clinical Features of Yellow Fever

Convalescent Phase

- Prolonged convalescence can occur with profound asthenia lasting 1 to 2 weeks
- rarely death occurs at the end of convalescence secondary to cardiac complications or renal failure
- elevation of LAE can persist for at least 2 months after onset of acute illness

- Diagnosis
  - PCR
  - positive serology (ELISA based assays, IgM in acute setting)
  - viral isolation can be done early while patient viremic

Treatment of Yellow Fever

- Isolation to prevent transmission to other patients via mosquitos
- No specific antivirals
- Supportive therapy as necessary
  - oxygenation
  - volume depletion

Yellow Fever Vaccine

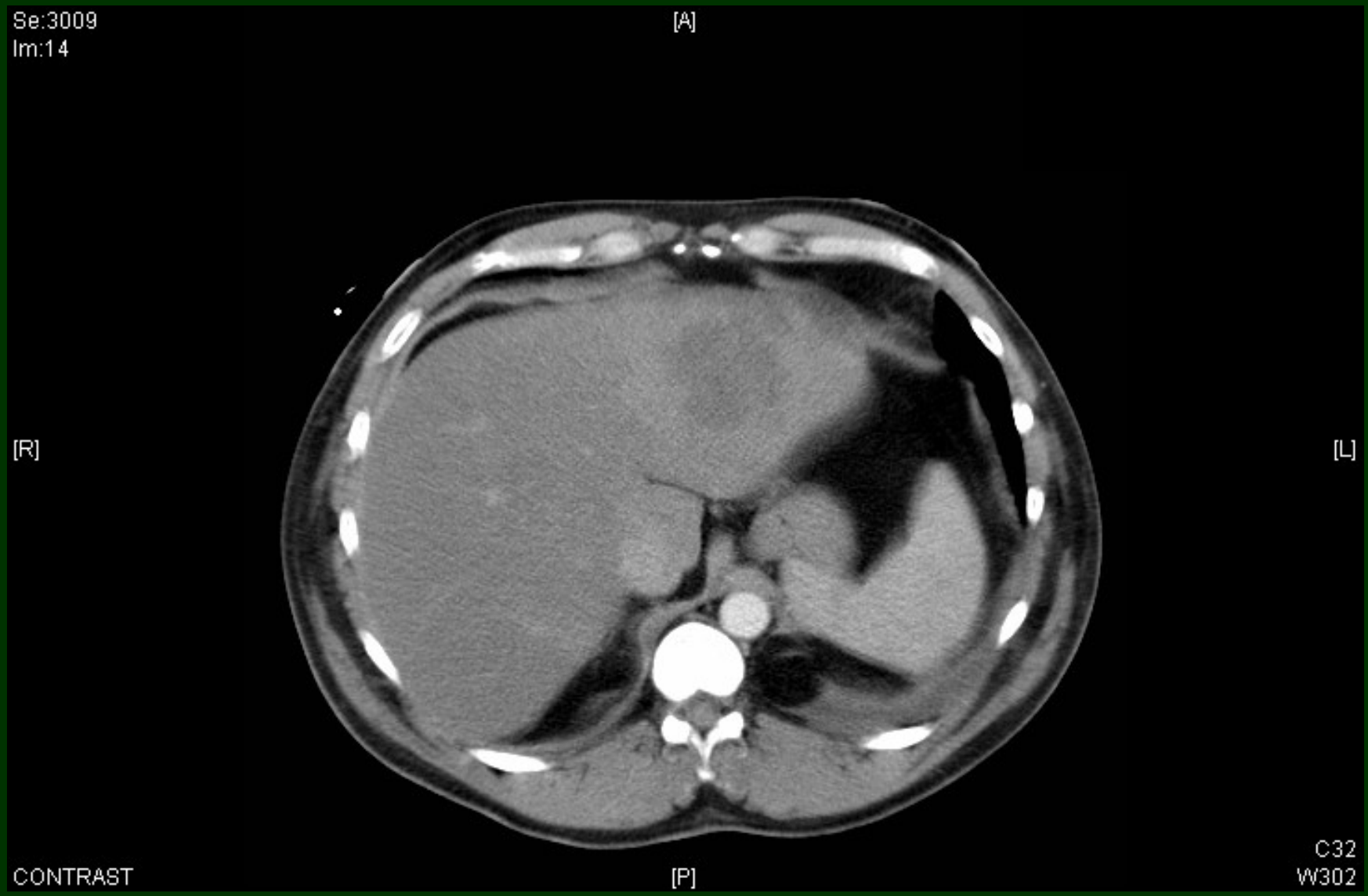
- live attenuated 17D virus
- effective and safe vaccine
  - over 8 million doses to U.S. travelers since 1965
  - 95% develop protective immunity (lifelong?)
  - 2-5% have headache, myalgias, low grade fever
  - < 1% curtail activities
  - anaphylaxis 1 in 130,000 (egg allergy)
- Rare fatal encephalitis in young (~20 cases reported)
- 1996-2001
  - 7 cases of multi-system organ failure after vaccination
  - SIRS response, no immunodeficiency in these patients identified

Case 3

- 50 y/o WM, SGM, presented with 5 days of abdominal pain, fever, and diarrhea.
  - abdominal pain diffuse, mild hematochezia attributed to hemorrhoids
- PMHx-
  - GERD (on prilosec)
  - heavy alcohol user
  - 30 pack year tobacco use

Case 3 (continued)

- Admitted
  - HR-136, T-102.3 F, ill appearing but in no acute distress
- Exam significant for no jaundice, no rash, diffuse abdominal pain, mostly in RUQ, hepatomegally, splenomegally
- Labs
  - WBC- 25,500 /mm^3 (27% band forms)
  - ALT- 139 IU/L, AST- 73 IU/L, Alk phos- 81 IU/L
- Treated for pyogenic liver abscess
  - imipenem 500 mg IV Q6 hours
  - no improvement, continued fever 4 days on ABX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CONTRAST
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Case 3 (continued)

- Incubation period?
  - traveled to El Paso 4 months ago, crossed boarder
  - one month stay in El Paso
- Vaccinations, prophylaxis?
  - Hep A and typhoid in 1998
- Food and water sources?
  - ate frequently at local food stands in Juarez, Mexico

Differential Diagnosis of Liver Lesion

- Pyogenic abscess: polymicrobial (GNR, anaerobes)
  - Older, multiple lesions, pos blood Cx, malignancy, GB disease
- Amebic liver abscess
  - Young, male, single lesion, right lobe of liver
- Echinococcal cyst
  - usually an incidental finding, atypical to cause fever
- Fascioliasis: infection with sheep liver fluke
- Syphilis: gumma
- Tuberculoma
- HIV: KS, Pneumocystis, Bartonella
- Other: hepatocellular cancer, metastatic cancer, hemangioma, lymphoma, cyst

Amebic Liver Abscess (ALA)

- Based on age, geography, single lesion, SUSPECT amebic
- Imaging can not differentiate amebic v. pyogenic
- Microscopic identification of parasite in stool, liver, pus
- Serology: 99% sensitive for liver abscess
  - Can’t differentiate between acute and remote disease
- Stool antigen detection kit
- Aspiration

Sensitivity of Tests for Diagnosis of Amebiasis

Test	Colitis	Liver Abscess
Microscopy		
Stool	25-60	10 to 40
abscess fluid	NA	<20
Antigen detection		
stool	90	~40
serum	65	~100
abscess fluid	NA	~40
Indirect hemagglutination (antibody)		
serum during acute illness	70	70-80
serum during convalescence	>90	>90

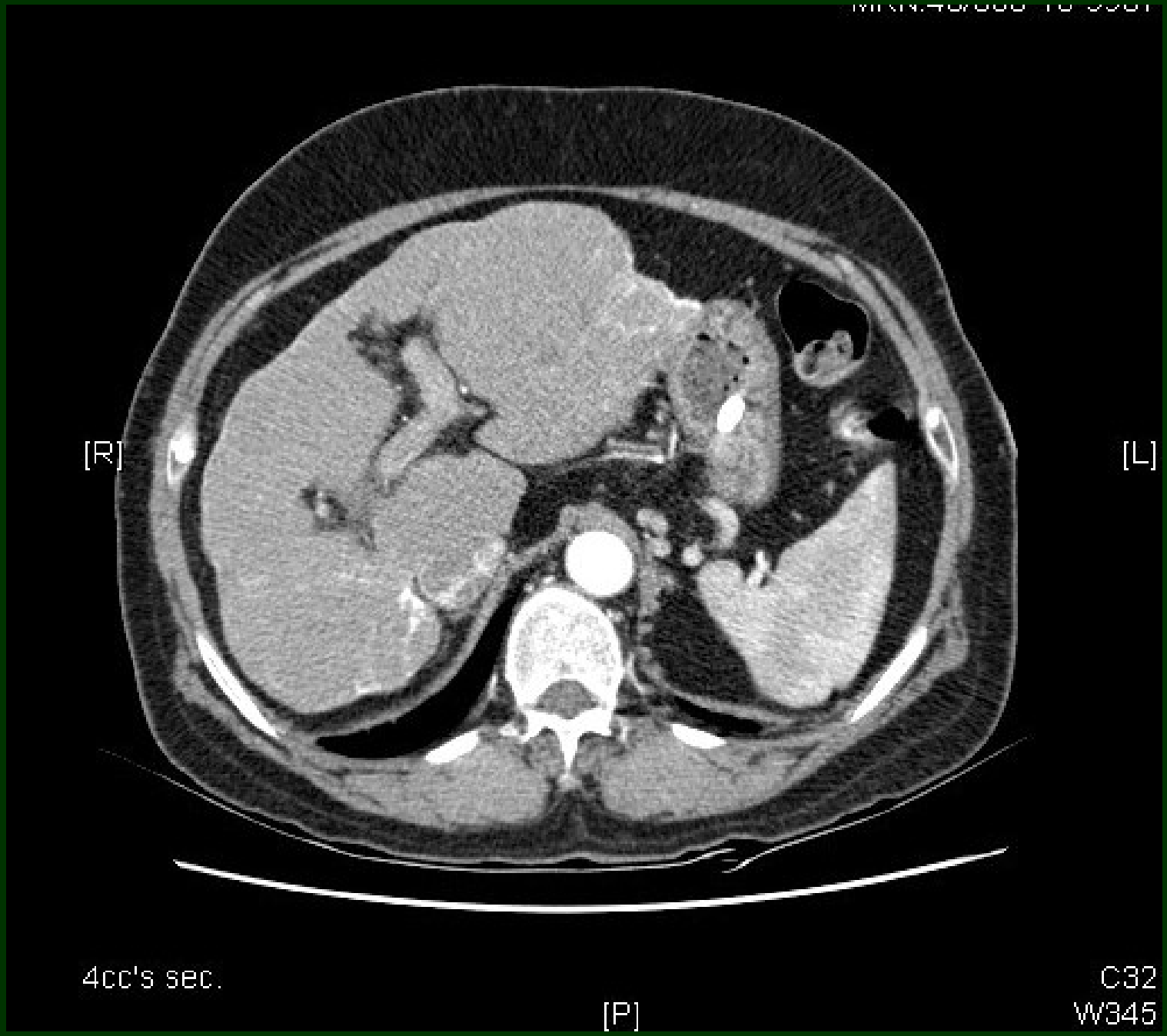
Haque R, "Amebiasis" N Engl J Med 2003;348:1565-1573

Treatment of ALA

- Differs compared to luminal, non-invasive amebiasis
- Abscess does not necessarily have to be drained
  - indications for drainage include failure to respond to antibiotics, cavity > 5 cm, lesion in left lobe of liver
- metronidazole 750 mg PO TID for 7-10 days
  - followed by a luminal agent (~50% still have parasites in gut)
  - paromomycin 25-35 mg/kg/day divided TID for 7 days

Case 4

- 55 y/o Filipino female with HTN, recently moved to USA from Philippines one month ago
- Presented to ER with left chest pain and SOB, and admitted for rule out MI
- ER work-up revealed an elevated D-dimer
  - CT angio showed no PE
  - abnormal liver on CT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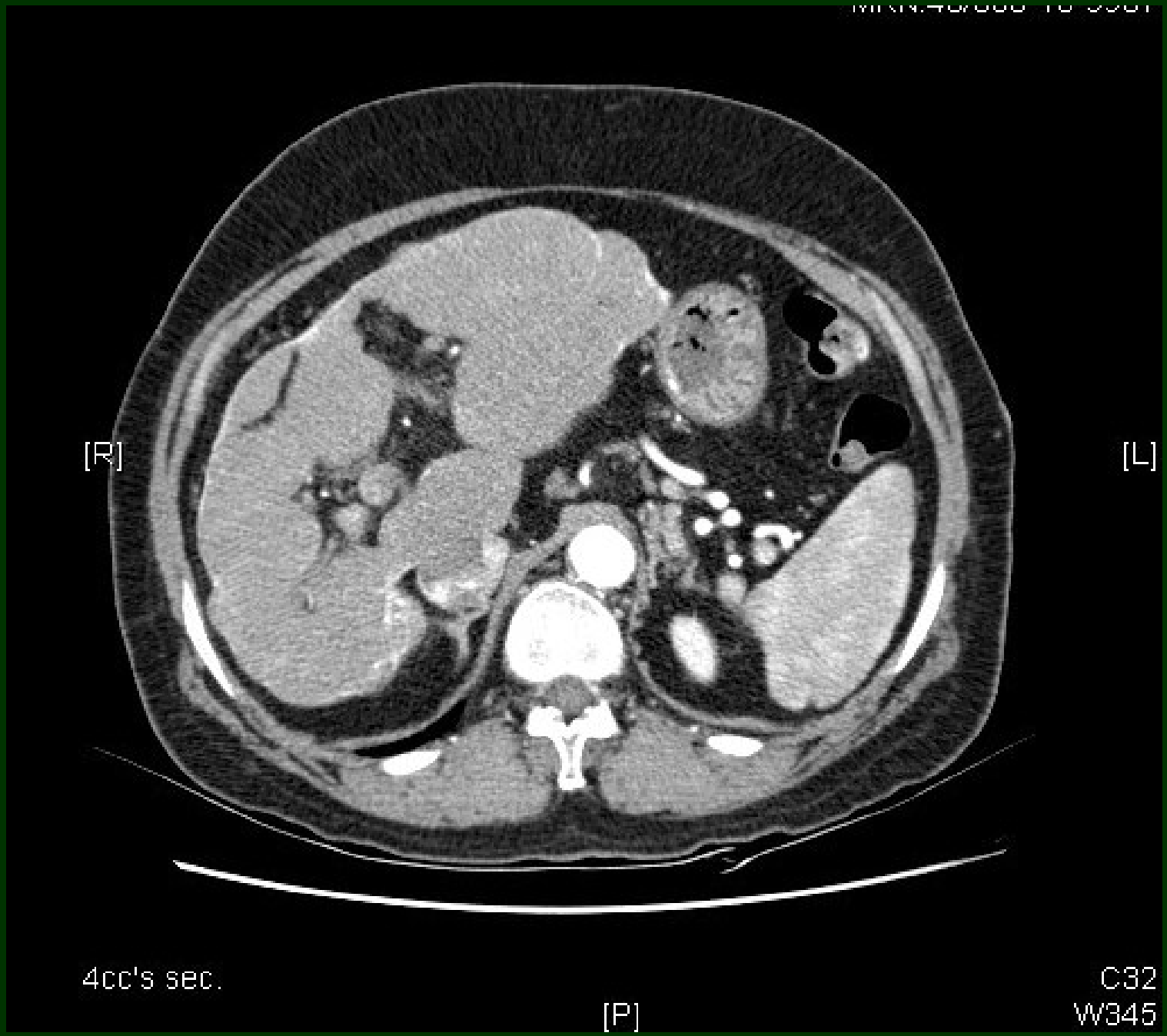
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Case 4 (continued)

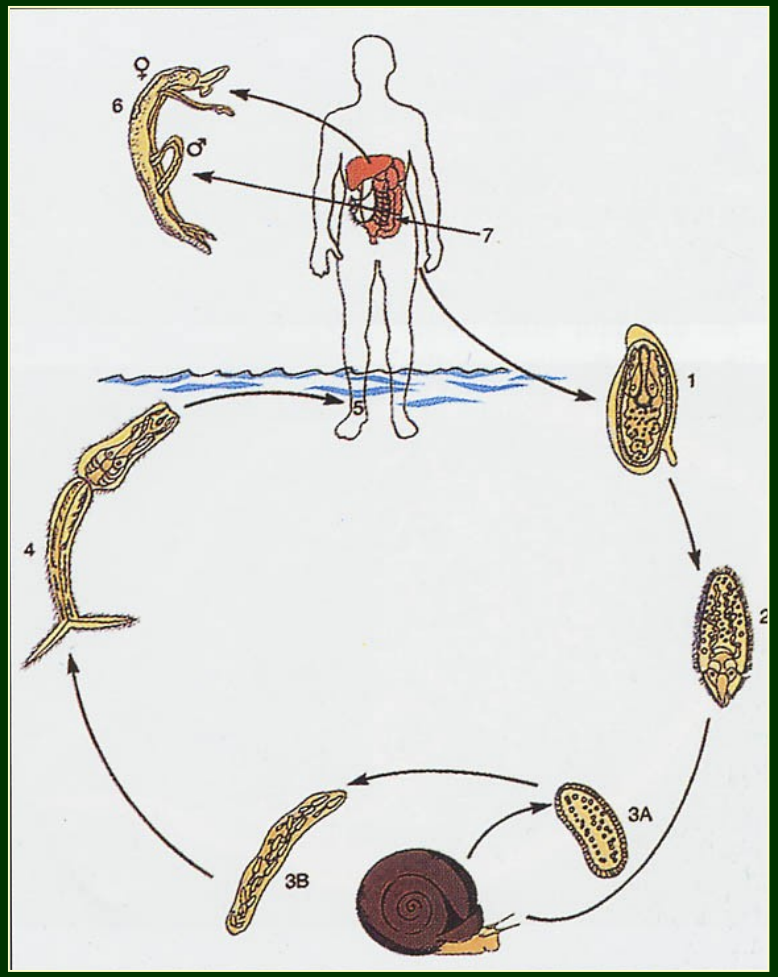
- Filipino, immigrated to U.S. 4 weeks ago
- No h/o liver problems or other PMH
- Many fresh water exposures
- ?itchy all over 10 years ago
- No h/o ascites, abdominal swelling, LE edema, jaundice, GI bleeds
- Treated for “worms” 15 years ago
- Meds: lisinopril, ASA
- NKDA

Case 4 (continued)

- Exam unremarkable. Abdomen soft, no mass, no tenderness. No palmar erythema, no telangectasiae
- No significant lab abnormalities, no elevation of LAE, normal bilirubin, normal synthetic function of liver

Schistosomiasis

- *Schistosoma mansoni*
- *Schistosoma japonicum*
- *Schistosoma haematobium*
- Widely distributed helminthic infection, worldwide
- Life cycle includes blood phase, tissue phase, and freshwater phase via snails



Schistosomiasis

- Immune response to larval and adult worms and eggs
  - focal granulomatous response
  - Katayama Fever—acute fever, chills, nausea, rash after exposure to cerariae. Eosinophilia.
- Chronic manifestations occur in the lung and liver, along with CNS manifestations with *S. japonicum*

Diagnosis and Treatment of Schistosomiasis

- History of being in endemic area, fresh water exposure
- Visualization of eggs in stool
  - serologic techniques available
- Treatment
  - praziquantel—60 mg/kg divided TID for one day
  - well tolerated, limited GI side effects, if any
- Prevention
  - DEET

Turtleback Liver

- Fibrotic reaction to chronic Schistosomiasis
  - egg and worm deposition in liver
- Treatment will not reverse fibrosis, but may decrease risk of future sequellae